A Dynamic Concept of Middle Cerebral Artery Occlusion and Cerebral Infarction in the Acute State Based on Interpreting Severe Hyperemia as a Sign of Embolic Migration

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SUMMARY The present study investigates the pathogenesis of focal cerebral hyperemia, its effect on brain tissue and discusses its pathophysiological and therapeutic importance in the light of interpreting severe hyperemia as a sign of arterial reopening probably due to embolic migration. Cerebral angiography, serial CT-scans and serial Tc-99m-scan were performed in a consecutive group of 73 patients with completed stroke all admitted to hospital within 3 days after stroke onset. When possible the regional cerebral blood flow (rCBF) was studied with the intracarotid Xe133 injection method. Twenty-nine patients had evidence of middle cerebral artery (MCA) occlusion; rCBF was investigated in 24. Fourteen patients had either occlusion or severe internal carotid artery (ICA) stenosis; rCBF was not measured in these patients. Thirty patients had no angiographical evidence of MCA occlusion, ICA occlusion or severe ICA stenosis; rCBF was investigated in 24.

Focal hyperemia was observed in 21 patients but exclusively in the group with evidence of MCA occlusion. Hence, these 21 patients are typical and representative for the group of patients with evidence of MCA occlusion. Hyperemia was found in infarcted as well as in non-infarcted tissue. Apparently, it is the severity of the initial ischemic episode and not the hyperemia that determines whether or not tissue necrosis develops. Interpreting severe arterial hyperemia as a sign of arterial reopening and embolic migration (evidenced by partial reopening affecting only some MCA branches) reopening had occurred in about half of the patients with MCA occlusion before they were examined 1 to 4 days after stroke onset. Autopsy studies performed in 8 of the patients with MCA occlusion indicate that arterial reopening also takes place in many patients later on (7 of 8). According to this interpretation, hypothetical as it is, the changing position of the embolus is associated with partial or complete reperfusion leading to hyperemia in the initially ischemic brain tissue. The hemodynamic basis for appropriate therapy therefore may change from one day to the next in the acute state of stroke due to MCA occlusion.

FOCAL CEREBRAL ISCHEMIA is the initial blood flow derangement after occlusion of a cerebral artery. When seen clinically on admission to hospital most infarcts are consequently thought to be low flow areas, perhaps with a rim of moderate hyperemia in the surrounding intact brain tissue due to diffusion of vasoreactive substances to the borderzone. Spontaneous reopening of the occluded artery, in the first hours or days, allowing early reperfusion of the ischemic area with a resultant high flow, is thought to be a fairly rare event.

Ischemia is thus considered to be the major blood flow abnormality in acute stroke when seen clinically. Nevertheless, focal hyperemia is an outstanding feature in the early stages after cerebral infarction. In a recent report of rCBF in acute stroke patients, all well visualized cortical infarcts were consistently associated with large areas of mild to severe hyperemia. The report focused on demonstrating this phenomenological aspect of acute cerebral infarcts, but a rather static concept of cerebral infarction in the acute state was retained — a concept comprising only two forms of cerebral infarcts: Infarcts that were totally ischemic, surrounded by a rim of hyperemic tissue, presumed to be caused by a stationary arterial occlusion and — less frequently — infarcts which were totally hyperemic considered to be caused by spontaneous recanalization of the occluded artery.

The present study was primarily carried out in order to investigate if cerebral hyperemia per se has a noxious effect on the brain tissue in acute stroke. However, the study of this problem led to the concept of interpreting the severe forms of hyperemia as a sign of arterial reopening and embolic migration and this became the main result of the investigation.

Material and Method

The present study is prospective and consecutive comprising a group of 73 patients with completed stroke. The patients were stroke patients below 75 years of age admitted to our hospital within 3 days after the acute onset of stroke. Excluded from the study were patients with: 1) strokes due to lesions in the brain stem and in the cerebellum; 2) Intracerebral hematomas; 3) TIA; 4) Myocardial infarction within 3 months of the stroke; 5) Insufficiency of heart, kidney and liver; 6) Severe disabling diseases as multiple sclerosis, advanced malignant diseases, severe dementia, previous disabling stroke etc., i.e. patients in whom we felt that a more specific diagnosis would not influence treatment and therapy. The study group comprised 47 males (mean age 63 years, range 47–75 years) and 27 females (mean age 67 years, range 44–75 years).

The investigation protocol was practically the same.
in all 73 patients: A full clinical neurological examination was performed on admission. Cerebral angiography and if possible investigation of the rCBF were performed within the first 24 hours after admission. The cerebral angiography and the rCBF investigation were not repeated later on. CT-scan was carried out one day later and repeated after approximately 2 weeks and 6 months. Tc<sup>99m</sup>-scintigraphy was performed within one week after the stroke and repeated approximately 2 weeks and 6 months after stroke. The protocol has been approved by the medical faculty, University of Copenhagen.

Cerebral Angiography

The patients were premedicated with diazepam 10 mg intramuscularly. Utilizing local anesthesia with 5 ml 1% Lidocain® the common carotid artery was punctured on the relevant side and the angiography was performed. CT-scan was performed with an EMI 1010 scanner using the 160 x 160 matrix. The first two examinations were performed with and without contrast administration while the third examination 6 months after stroke was performed only without contrast administration. Tc<sup>99m</sup> scan was performed using a scintillation camera equipped with a high resolution converging collimator. 15–20 mCi technetium-99m pertechnetate was injected intravenously. The brain imaging was usually performed 1½–2 hours after the injection. rCBF was studied using the intracarotid Xenon-133 injection method just after cerebral angiography was performed using the same catheter. A 254 multidetector scintillation camera and the initial slope analysis was used to measure the blood flow. The data are presented as absolute values on a teletype or as a schematic two-dimensional picture of the brain with 254 colour squares each representing an interval of flow values on a 16 level colour scale (fig. 1).

Focal hyperemic areas were defined as areas where rCBF was increased more than 20% (left hemisphere) respectively more than 26% (right hemisphere) above the mean hemispheric CBF. This is 3 times the coefficient of variation seen in 24 normal patients (Larsen et al. 1978). In this group the mean hemisphere blood flow was 55 ± 4.8 ml/100 gr/min. in the right hemisphere and 49 ± 3.2 in the left hemisphere. Hence, corresponding to p < 0.01 absolute hyperemia was considered to be blood flow >69 ml/100 gr/min. in the right hemisphere and >59 ml/100 gr min. in the left hemisphere.

Autoregulation was tested by increasing the blood pressure 20 to 40 mm Hg during continuous intravenous infusion of angiotensin. The blood pressure was measured continuously via the carotid catheter. Immediately after the injection of Xe<sup>133</sup> a blood sample for pCO<sub>2</sub> determination was taken. CO<sub>2</sub>-response was tested during spontaneous hyperventilation or during inhalation of 5% CO<sub>2</sub>. Autoregulation was considered impaired if induced hypertension increased the blood flow more than 12.2%. This is 2.26 times the coefficient of variation seen with this test in 9 normal subjects and hence corresponds to p = 0.05. Autoregulation was considered false if induced hypertension decreased blood flow more than 12.2% or if induced hypotension did not increase the blood flow more than 12.2% in regions with impaired CO<sub>2</sub>-response. CO<sub>2</sub>-response was considered impaired if the blood flow did not change during spontaneous hyperventilation or during inhalation of 5% CO<sub>2</sub>.

Cardiac Diseases

All patients were examined for atrial fibrillation and previous myocardial infarction. ECG was performed in all.
Autopsy Studies

Nine of the patients with angiographically verified MCA occlusion died within a period of 3 years after stroke. An autopsy was performed in 8. The main trunk and the proximal part of the major branches were searched for thromboembolic material and atherosclerotic lesions corresponding to the angiographical site of occlusion.

Description of the Study Population According to Cerebral Angiography, CT-Scan and Cardiac Examination

Angiographically the 73 patients were divided into 3 main groups:

I) 29 Patients With Evidence of MCA Occlusion

Twenty-one had MCA occlusion alone, 5 had MCA occlusion associated with severe ICA stenosis with or without intraluminal non-occluding thrombus formation. Three had prominent early filling veins as the only abnormal angiographical finding explaining the stroke (we consider early filling veins to indicate reopening of previously occluded arteries). In addition to these 3 patients, early filling veins occurred in another 8 of the patients having at the same time verified occlusion in the MCA territory.

Most of these patients had major clinical symptoms and had on CT-scan relatively large infarcts which commonly involved the cortical convexity structures: Fourteen had large infarcts with a diameter >3 cm, 14 were medium sized infarcts with a diameter between 1.5 cm and 3 cm and 1 patient had no infarct on CT-scan. Nineteen of these infarcts involved also cortical convexity structures while 9 were exclusively located deeper in the hemisphere.

Twelve of the patients in this group had atrial fibrillation and/or previous myocardial infarction (AF/MI). Hence, taken together with the 5 patients with MCA occlusion combined with significant ICA lesion a total of 17 of the 29 patients (59%) had a likely embolic source in the heart or in the ICA.

Of the 21 patients with MCA occlusion alone 4 had slight to moderate ICA stenosis, 12 had non-stenosing ICA atherosclerosis and 5 had a normal ICA. The ICA was not considered to be an embolic source with a reasonable degree of certainty in these patients. Only 8 of the 30 patients (27%) had AF/MI as a possible embolic source.

2) 14 Patients with Either ICA Occlusion (9 Patients) or ICA Stenosis of more than 75% of the Lumen (5 Patients) as the Most Likely Cause of Stroke

Most of these patients had major clinical symptoms and the infarcts were relatively large and commonly involved cortical convexity structures: Six had large infarcts with a diameter >3 cm, 6 had medium sized infarcts with a diameter between 1.5 cm and 3 cm, 1 had an infarct with a diameter <1.5 cm and 1 patient had no infarct on CT-scan. Nine of these infarcts involved cortical convexity structures while 4 were located deep in the hemisphere.

Only two of these patients had AF/MI as a possible embolic source. However, because of the total occlusion and because of insufficient filling of the intracranial vessels in the 5 patients with severe ICA stenosis the ICA cannot be ruled out as a source of possible distal embolism.

3) 30 Patients Without Evidence of MCA Occlusion, ICA Occlusion or Severe ICA Stenosis (The Cause of Stroke Thus Being Angiographically Unexplained)

These patients had minor clinical symptoms and had relatively small infarcts or had no infarcts on CT-scan. The infarcts were always located deep in the hemisphere never involving cortical convexity structures: Five had medium sized infarcts with a diameter between 1.5 cm and 3 cm, 14 had small infarcts with a diameter <1.5 and 11 patients were without infarcts on CT-scan.

Nine patients had a moderate to slight ICA stenosis, 14 patients had non-stenosing ICA atherosclerosis and 7 had a normal ICA. The ICA was not considered to be an embolic source with a reasonable degree of certainty in these patients. Only 8 of the 30 patients (27%) had AF/MI as a possible embolic source.

Comments on CT-scan and Tc⁹⁹-scan

The diagnosis of a cerebral infarct was based on the demonstration of a hypodense area on CT-scan and further confirmed by the demonstration of contrast enhancement and Tc⁹⁹-pertechnetate accumulation in corresponding areas.

When a hypodense area was seen in the early CT-scan it was in all cases also found on the late CT-scan performed 6 months later and the size was practically the same regardless of what the result of the rCBF investigation had been, i.e. ischemic or hyperemic infarction. Because of the so-called “fogging effect” whereby hypodense lesions become transiently isodense or close to isodense during the second and third week after the stroke most of the infarcts appeared considerably smaller or they were even not identifiable on CT-scan in that period. In the same period the infarcts were, however, visualized by contrast enhancement. Areas that exhibited contrast enhancement in the second CT-scan were always hypodense on the CT-scan 6 months after the stroke.

Hemorrhagic infarction was only observed on CT-scan in one patient (2 weeks post stroke). It was not observed in any of the early CT-scans performed the day after the angiography irrespective of the presence of a hyperemia or not. It should be emphasized that the rare demonstration of hemorrhagic infarcts on CT-scan in this series probably does not reflect the incidence of hemorrhagic infarction. It rather reflects the technical inability to demonstrate the phenomenon on CT-scan. Hemorrhagic infarcts are characterized by perivascular petecchial bleeding primarily localised in the cortical grey matter — true hematomas are seldom seen. The density recorded by the CT-scanner is an average density of the high density in the petecchial bleeding and the low density in the surrounding tissue. Depending on the degree of petecchial bleeding and
the degree of low density in the surrounding tissue a hemorrhagically infarcted tissue may appear hypodense, isodense or hyperdense. Therefore it is difficult to delineate hemorrhagic infarcted tissue from neighbouring normal and ischemic infarcted tissue.

The results of Tc""-scanning appeared to depend upon the location and the size of the infarcts.26 Small deep infarcts were practically not demonstrated by Tc""-scans while the large infarcts nearly always were demonstrated. As the results appear in a lateral projection of the brain the Tc""-scans were fairly easy to correlate with the flow maps which also appear in that projection.

**Results**

rCBF was measured in 48 of the 73 patients. Focal hyperemia was recorded in 21 patients. The 48 patients in whom rCBF was recorded were distributed among the angiographical subgroups as follows:

1) Twenty-four of the 29 patients with evidence of MCA occlusion. rCBF was not measured in 3 patients with concomitant severe ICA disease and in 2 patients because of technical difficulties in catheterizing the ICA. Focal hyperemia was recorded in 21 of the 24 patients (84%) thus being exclusively seen in this group. 2) None of the 14 patients with ICA occlusion or tight ICA stenosis. 3) Twenty-four of the 30 patients without evidence of MCA occlusion, ICA occlusion or severe ICA stenosis. rCBF was not measured in 2 patients because of moderate ICA stenosis and in 4 patients because of technical difficulties in catheterizing the ICA. Focal hyperemia was not recorded in any of these 24 patients.

The location of the hyperemic and the ischemic areas on the flow map in the 21 patients with focal hyperemia and the location of the infarcts as revealed by hypodense and contrast enhanced areas on CT-scan and isotope accumulation on Tc""-scan are shown in table 1. The time interval from the stroke to these investigations were performed appears also from the table. The CT-scans and the Tc""-scans performed 6 months after the stroke are not shown. The degree of hyperemia and the vascular reactivity in the hyperemic areas (autoregulation and CO2-reactivity) are presented in table 2. Age and sex appear also from table 2.

**Patients with Hyperemia: Location and Type of Hyperemia Related to Infarction and Arterial Occlusion**

**A1: Severe Hyperemia Due to Complete Arterial Reopening After an Infarct is Established**

Two patients (cases 1 and 2) had hyperemic areas in the MCA territory, areas that were coexistent with the entire hypodense region on the CT-scan (table 1). Both areas subsequently showed abnormal isotope accumulation on Tc""-scan (figs. 1, 2). In case 1 the hyperemic area also showed contrast enhancement on the second CT-scan taken 14 days after stroke onset, while this was not seen in case 2. But, in this case the second CT-scan was taken on day 30 and it may well be too late for visualising the abnormal permeability. Cerebral angiography showed no arterial occlusion while prominent early filling veins occurred in areas corresponding to the hyperemias seen on the flow maps. Patient 1 had atrial fibrillation. An embolic source in the ICA was not demonstrated in these patients.

Cerebral blood flow was very high in the hyperemic areas ranging far above the flow level defining absolute hyperemia. Both hyperemic areas were characterised by false autoregulation and abolished CO2-reactivity reflecting a state of complete vasoparalysis due to severe tissue damage (table 2).

Because of hyperemia in an infarct with angiographical evidence of a prior occlusion we interpret these two patients as representing complete spontaneous reopening of the MCA — a reopening coming too late to avoid complete ischemic infarction.

**A2: Severe Hyperemia Due to Incomplete Arterial Reopening — Embolic Migration — After an Infarct is Established**

Three patients (cases 3–5) had hyperemic areas in the MCA territory that were partially coexistent with the infarcts on CT-scan as these areas subsequently showed enhanced contrast and isotope uptake. In two this was seen on the second contrast enhanced CT-scans (the study was not carried out in the third case). Tc""-scans showed in all three cases that the isotope uptake was most intense over the hyperemic border-zone outlining nearly the very same areas (table 1, figure 1, 2). The hyperemias had a location corresponding to the supply area of one or two large MCA branches identifiable on the angiograms. The remainder of the infarcts were ischemic on the flowmap. Early filling veins were observed in topographical relation to the hyperemic zone while the arteries normally supplying the ischemic area were occluded. Patient 3 and 5 had atrial fibrillation. Patient 4 had a nonoccluding thrombus formation in the ICA as the likely embolic source. An embolic source in the ICA was not demonstrated in patients 3 and 5.

The blood flow reached very high values in the hyperemic areas, values ranging above the flow level defining absolute hyperemia. The vascular reactivity was impaired or false (table 2).

Because of severe hyperemia inside the peripheral part of these infarcts with angiographical evidence or prior occlusion of the arteries supplying the hyperemic area and of persistent occlusion of the arteries normally supplying the ischemic area we interpret these three patients to represent migration of the occluding material with reopening of some (proximal) MCA branches, a reopening coming too late to avoid infarction of the revascularized part of the infarct.

**B: Severe Hyperemia Due to Arterial Reopening Before an Infarct is Established**

Three patients (cases 6–8) had severe hyperemia in areas with persistently normal density on CT-scan. The Tc""-scans and the contrast enhanced scans remained also normal in these areas (table 1, Figure 1, 2).

The three patients had all prominent early filling...
veins that were draining the hyperemic areas. Occlusions were not seen in the arteries supplying the regions. Patient 8 had previous myocardial infarction. An embolic source was not demonstrated in the ICA in these three patients.

The blood flow levels were very high in the hyperemic areas — in all three patients ranging far above the level defining absolute hyperemia. But, contrary to the above mentioned groups the vascular reactivity was normal (table 2).

Patient 6 had neurological deficits for 3 to 4 days (aphasia) after which neurological recovery was complete. The CT-scans in this patient was completely normal. Patients 7 and 8 had persistent symptoms attributable to the visualized arterial occlusions and the corresponding infarcts that were located at a distance from the hyperemias while persistent symptoms attributable to lesions in the hyperemic areas were not observed. Neuropsychological examinations also failed to reveal deficits attributable to lesions in these hyperemic areas. Thus, in all three recovery of function appeared to be complete in the hyperemic areas.

Because of severe hyperemia in a non-infarcted area with angiographical evidence of a prior occlusion we interpret these three patients as representing spontaneous reopening of the MCA occurring before ischemic necrosis had time to evolve. In patient 3 reopening has been complete while the embolus probably have migrated more distally in patient 4 and 5 as occlusion and corresponding infarction were seen in both patients more distally in the MCA territory (table 1).

C: Mild Hyperemia Due to a Stationary Occlusion

Eight patients (cases 9–16) had moderately hyperemic areas localised in the borderzone of or close to the borderzone of a low flow area that corresponded to a cortical infarct on CT-scan.

Cerebral angiography showed MCA occlusion in all

<table>
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<tr>
<th>Group</th>
<th>Case</th>
<th>CT-scan I Low density area</th>
<th>rCBF Hyperemia, ischemia</th>
<th>Brain-scintigraphy I</th>
<th>CT scan II Enhanced areas</th>
<th>Brain-scintigraphy II</th>
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hemodynamics in acute cerebral infarction/olsen and lassen

cases. five had trunk occlusions and three had branch occlusions. two patients had atrial fibrillation and another two had previous myocardial infarction. none of the patients had evidence of an embolic source in the ICA.

Cerebral blood flow was only moderately increased in the hyperemic areas. The flow values ranged below the level defining absolute hyperemia. one patient showed impaired autoregulation in the hyperemic area. the vascular reactivity was normal in the remaining patients (table 2).

Because the mildly hyperemic areas most likely were located outside the infarct in areas without angiographical evidence of prior occlusion we interpret these patients as probably representing cases of stationary occlusion. the borderzone of mild hyperemia in the surrounding intact brain tissue might be due to diffusion of vasoactive metabolites from the ischemic infarct. in three patients, however, (cases 9, 12, 16) the hyperemia area was confined to the territory of the anterior cerebral artery (ACA) (table 1). Because hyperemia is defined on a statistical basis it is possible that mild hyperemia in these patients become statistically significant merely because of the coexisting large low flow areas (the "occluded" MCA territory). the hyperemias therefore might represent the most normally perfused part of the brain in these patients, i.e. the ACA territory.

D: Mild and Remote Hyperemia of Uncertain Origin

Five patients with deep infarcts had mild hyperemia located remote from the infarcts in areas with persistently normal density on CT-scan and Tc99m-scan (table 1).

These 5 patients had neither early filling veins nor arterial occlusions in the corresponding hyperemic areas. All 5 patients had deep infarcts corresponding to occlusions of the MCA territory in which the infarcts were located. Two had trunk occlusions and three had branch occlusions. Patient 17 had a previous myocardial infarction and atrial fibrillation, patient 19 had a non occluding thrombus formation in the ICA as the likely embolic source. In the remaining 4 patients an embolic source was not demonstrated in the ICA.

The blood flow was only moderately (relatively) increased in the hyperemic areas ranging below the levels defining absolute hyperemia. Vascular reactivity in the hyperemic areas was normal in three and impaired in two (false) (table 2). The occluded areas were in these patients supplied by collateral circulation mostly in the form of retrograde filling from the ACA. Because hyperemia is defined on a statistical basis they
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TABLE 2  Blood Flow and Vascular Reactivity in 21 Stroke Patients with Focal Cerebral Hyperemia

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<th>Autoregulation</th>
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*Not performed.

might represent the most normally perfused part of the brain.

Because of the localization deep in the hemisphere it is a priori impossible to visualise these deep infarcts with the two-dimensional rCBF technique due to tissue absorption of radiation,11 "the look through phenomenon"27 and Compton scatter.28, 29 Hyperemia, if associated with these deep infarcts, would probably be located mostly in the white matter in which the blood flow normally is 3 to 4 fold lower than in the grey matter. It is therefore unlikely that hyperemia confined to white matter could be detected "through" the cortical mantel even if the hyperemia was 100% and 300% above normal values.

Patients Without Hyperemia

Twenty-seven patients (cases 22 to 48) had no hyperemia. Three of these had MCA occlusion. The remaining 24 comprised the entire group of patients without angiographical evidence of MCA occlusion in whom an rCBF investigation was performed. All these 27 patients had either relatively small and deeply localised infarcts or no infarcts on CT-scan or Tc99 scan.

Because of the localization deep in the hemisphere and because of their small size it is a priori impossible to visualise these infarcts with the two dimensional rCBF technique used in the present study.

Correlation Between Cerebral Angiography and Autopsy

Nine of the patients with verified MCA occlusion died within a period of 3 years after the stroke. An autopsy was performed in 8. The main trunk and the proximal part of the major branches of the MCA were routinely searched for thromboembolic material. In only one patient who died one week after the stroke, the occluding material was found at a site corresponding to the occlusion on the angiogram. In the remaining 7 patients who died 1 week, 6 weeks, 3 months, 3 months, 20 months, 23 months and 34 months after the stroke the occluded artery was found to be patent on autopsy. Stenotic/atherosclerotic lesions corresponding to the angiographical site of occlusion were not observed on autopsy in any of the patients.

Discussion

Representativity of and Cause of Stroke in the Study Population

Because hyperemia was so common in the patients with evidence of MCA occlusion (21 of 24 patients with rCBF recordings) and because hyperemia exclusively was found in this group of patients the 21 patients not only represent a selection of stroke patients with focal hyperemia, they also represent very closely the entire group of patients with angiographical evidence of MCA occlusions in our study population.
Hence, the conclusions and the hypothesis developed on the basis of an analysis of the hyperemias apply to practically the entire MCA group and thereby essentially to stroke of embolic origin (see below). They do not apply to stroke patients without angiographic evidence of MCA occlusion, viz. to stroke patients with small deep infarcts (that in our series practically all had a size and a localization of a lacunar infarct) or to stroke patients with ICA occlusion: the stroke types known to be primarily caused by thrombosis, not embolism.

The study group represents a consecutive series comprising all acute stroke patients below the age of 75 years admitted over a period of 15 months. The attitude to the stroke disease is traditionally an active one in our hospital. Carotid endarterectomy, anticoagulation therapy and surgical evacuation of a hematoma are considered in all stroke patients of the age group mentioned above. As a CT-scanner is not available in our hospital cerebral angiography is considered to be without diagnostic and/or therapeutic relevance. It may also be noted that our hospital is a large municipal hospital serving as the only hospital a fixed population of 200,000 citizens living in a well defined area of Copenhagen. We therefore consider major sampling bias to be unlikely.

Embolism is considered the likely cause of acute MCA occlusive disease present in 40% of the population studied. This conclusion accords with the generally held opinion that spontaneous arterial reopening seen in many of our MCA patients is much more frequent with embolism than with local thrombosis. It also accords with the fact that no less than 59% of the MCA patients had a likely embolic source in the heart or the neck arteries against 20% of the patients without evidence of MCA occlusion. Finally it accords with the post mortem findings. In all 8 autopsy studies the wall of the MCA, at the site of prior (7 cases) or persisting (1 case) occlusion, was devoid of athero-
sclerosis or other abnormalities, a finding which agrees with the neuropathological experience that in situ thrombosis is rare in the MCA.17, 36, 39, 40

Focal Hyperemia: Effect on the Brain Tissue and Pathophysiological Considerations

Severe Hyperemia Does not Lead to Cell Necrosis

Basing the diagnosis of infarcted tissue on both CT-scan and Tc99m-pertechnetate scintigraphy it was evident that severe hyperemia in several cases (group A) was located to areas that underwent infarction. However, three patients (group B) with extensive and severely hyperemic areas developed neither hypodensity nor subsequent CT-enhancement or Tc99m accumulation in the corresponding areas. The vasomotor responses were also normal and persistent neurological deficits attributable to lesions in these hyperemic areas were not observed. It is therefore unlikely that hyperemia per se has a noxious effect on brain tissue subsequently leading to the development of tissue necrosis.

Severe Hyperemia, a Sign of Spontaneous Arterial Reopening and Embolic Migration

An interrelationship must nevertheless exist between hyperemia and infarction because a particular vasoparalytic form of hyperemia was consistently associated with enhancement and isotope uptake on subsequent CT- and Tc99m-scans: Five patients (group A) had focal hyperemias characterized by a very high blood flow level, by impaired vascular reactivity and by angiographical evidence of vascular recanalization (early veins). These vasoparalytic hyperemic areas developed infarction of the very same areas. As argued above hyperemia per se is unlikely to damage brain tissue to such a degree that tissue necrosis develops. We therefore hypothesize that ischemia existed in these areas before the hyperemia developed. This has led us to a more dynamic concept of cerebral infarction due to MCA occlusion than the rather static one mentioned in the introduction: During the first hours or days after an occlusion the same cerebral infarct may assume different forms. 1) an occlusion gives rise to an ischemic infarct surrounded by a rim of intact but mildly hyperemic tissue. II, within the following hours or days the embolus migrates more peripherally in the vascular tree allowing reperfusion and marked hyperemia in the peripheral part of the infarct. III, within the next hours or days the emboli may even disintegrate completely changing the entire infarct into a hyperemia.

FIGURE 3. A schematically illustration of the dynamically changing infarct. During the first hours or days after the stroke the same cerebral infarct may assume different forms. 1. an occlusion gives rise to an ischemic infarct surrounded by a rim of intact but mildly hyperemic tissue. II, within the following hours or days the embolus migrates more peripherally in the peripheral part of the infarct. III, within the next hours or days the emboli may even disintegrate completely changing the entire infarct into a hyperemia.

We could not perform serial angiography and therefore we cannot visualize arterial recanalization and embolic migration. However, we cannot find any other way to explain the occurrence of severe hyperemia in this series. Abundant evidence of such a development is accumulated in the literature and the following other possible explanations can be ruled out: 1) The severely hyperemic areas cannot be collaterally perfused areas: The early filling veins draining the hyperemic areas were not localized distal to the occlusion as would be expected if these areas were collaterally perfused — they were localized proximal to the occlusion. The angiograms as well as the isotopangiograms obtained in connection with the flow study clearly showed that the areas were filled anterogradely and as expected very rapidly. Collaterally perfused areas in patients with MCA occlusion moreover appears to be low flow areas rather than hyperemic areas in the acute state. 2) The severely hyperemic areas cannot be due to vasoactive metabolites leaking out from the infarcts: In the three patients with infarcts considered to be partially reperfused the hyperemias were localized exclusively according to the vascular anatomy of the large arteries — arteries which were identifiable on the angiograms. The hyperemias did not surround these infarcts ignoring the large artery anatomy as would be expected if leaking out of metabolites from the infarcts were responsible for the hyperemia. 3) The severe hyperemic areas cannot be granulation tissue absorbing necrotic brain tissue: Two patients had extensive hyperemias in infarcted brain tissue which were seen on rCBF examinations as early as 8 hours (patient 1) and 24 hours (patient 5) after the stroke. Granulation tissue combined with impaired vascular reactivity most likely reflects severe ischemic damage completed before partial reperfusion took place rather than a noxious effect of hyperemia.

The finding of vasoparalysis in the 3 cases with severe borderzone hyperemia was in our previous analysis49 taken to indicate the noxious effect of hyperemia on brain tissue. According to the present evaluation this is not a correct interpretation. The high blood flow...
cannot develop and affect areas of such an extension so quickly. Furthermore 3 patients had large hyperemic areas in which evidence of tissue necrosis did not develop.

**Mild Hyperemia in Patients with Stationary MCA Occlusion**

Eight patients (group C) had mild hyperemia in the borderzone or near to the borderzone of infarcts with cortical involvement. In contrast to the above mentioned 8 patients these hyperemias were of a moderate degree, showed no angiographic evidence of arterial reopening and five of the eight had MCA trunk occlusions — lesions not found in the former 8 patients except for the patient where reopening affected the anterior cerebral artery (case 7). The vascular reaction was intact except for one patient and abnormal contrast enhancement or isotope uptake did not develop. We therefore hypothesize these infarcts to be the result of a stationary occlusion — disintegration and/or embolic migration of the occluding material have not (yet?) taken place and reperfused severely hyperemic areas have not (yet?) developed.

**Frequency and Timing of Spontaneous Arterial Reopening in MCA Occlusion**

Among the 24 flow studies in patients with angiographic signs of MCA occlusion no less than 8 showed evidence of spontaneous reopening of occluded arteries in the period from 1 to 4 days after the stroke. Nine of the 24 patients had infarcts not involving the superficial cortex and comprise a special category of patients as two-dimensional rCBF method is ill suited to study. Hypotheses due to arterial reopening are therefore easily overlooked in these patients. Hence, our findings suggest early spontaneous reopening of occluded arteries to occur in at least ½ of patients with signs of MCA occlusion in the present series. Recanalization at a later state is also quite frequent. This is amply demonstrated in studies on patients undergoing serial angiography and correlative studies of cerebral angiography and autopsies including our own in which 7 of 8 patients studied had evidence of arterial reopening.

Fisher and Adams 1950 advanced a very similar hypothesis based on interpreting partial or complete hemorrhagic infarcts as the result of embolic migration. They also considered the phenomenon to be quite common. Hemorrhagic infarcts are nearly always of embolic origin and embolic infarcts are in autopsy materials hemorrhagic in about ½ of the cases. As the majority of MCA occlusions appear to be of embolic origin it is not unlikely that hemorrhagic infarcts and hyperemia are manifestations of the same pathophysiological process — embolic migration.

If the hypothesis presented here is true, it might be of significance for the timing of therapy. According to the hypothesis the hemodynamic situation around and within the infarct changes spontaneously. An attempt to increase blood flow to an acutely occluded and ischemic area seems reasonable while it is meaningless and possibly harmful if the artery has already reopened and the previously ischemic area has become hyperemic.

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